Investigation of the role of O-GlcNAcylation in SOX2 function during reprogramming

Grant Award Details

Investigation of the role of O-GlcNAcylation in SOX2 function during reprogramming

Grant Type: Basic Biology IV

Grant Number: RB4-05990

Project Objective: The PI has previously found that in murine embryonic stem cells, the transcription factor SOX2 is modified by the OGT enzyme, which is essential in the glucose nutrient-sensing pathway. This modification affects SOX2 function during reprogramming to pluripotency and self-renewal, and the goals of this project are to elucidate the molecular mechanisms that underlie these observations, and to determine whether the modification functions similarly in human iPSCs.

Investigator:

Name:	Barbara Panning
Institution:	University of California, San Francisco
Type:	PI

Human Stem Cell Use: iPS Cell

Award Value: $1,285,214

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Investigation of the role of O-GlcNAcylation in SOX2 function during reprogramming

Public Abstract: Induced pluripotent stem cells (iPSCs) are a potential source of material for cell replacement therapies. Thus, achieving maximal efficiency of reprogramming will be important for cellular medicine. In this submission we propose to test whether manipulating the mammalian glucose sensing pathway. The enzyme OGT is part of the glucose-sensing pathway and is necessary in pluripotent cells. OGT catalyzes the transfer of a sugar to target proteins, which regulates protein function. This transfer is the terminal step in the hexosamine signaling pathway (HSP). The HSP serves as a nutrient sensor, as the concentrations of the sugar donor used by OGT fluctuate with glucose levels. As a result, changes in intracellular glucose concentration cause alterations in modification of OGT target proteins. This nutrient-responsive signaling system modulates important cellular pathways, including the insulin-signaling cascade. Alterations in OGT activity are associated with diabetes mellitus and Alzheimer's disease. Thus, our studies of role of OGT and the HSP in self-renewal and reprogramming may also shed light on the role of this pathway in other stem cells, such as neuronal and islet stem cells, whose depletion may contribute to these degenerative diseases. Understanding the role of OGT in ESCs and iPSCs will both increase our knowledge of the molecular mechanisms mammalian cells use to establish and maintain pluripotency and perhaps lead increase the efficiency of reprogramming.

Statement of Benefit to California: Among ten leading death causes in California, five of them can directly benefit from cell-based tissue regeneration. These include heart disease, stroke, Alzheimer's disease, diabetes, and liver diseases. Currently, the economic burdens derived from these diseases are enormous. It is estimated from State of California, Department of Public Health that California taxpayers pay 48 billion dollars annually for cardiovascular diseases, 73 billion dollars excluding non-paid family care for Alzheimer's disease, and 116 billion dollars for diabetes-related diseases. Induced pluripotent stem cells (iPSCs) offer great promise as tools for regenerative medicine. However, the iPSC technology still has several shortcomings inhibiting its clinical application, one of which is the low efficiency in production iPSCs. The research outlined in this application has the potential to provide a method that substantially increases the efficiency of production of human induce iPSCs. If these studies lead to improvements in the production of iPSCs, facilitating their use in regenerative medicine, they will directly benefit the health of California citizens and reduce the economic burden presently borne by California taxpayers. This research may increase California's visibility in stem cells research and attract federal funding to sponsor future research. It may also enhance California's economic growth by stimulating the iPSC regenerative medicine industry for the treatment or cure of diseases.